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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/381,497	02/17/2000	DAVID J. FITZGERALD	015280-317100US	4036

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EXAMINER

TUNGATURTHI, PARITHOSH K

ART UNIT	PAPER NUMBER
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1643

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08/07/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 09/381,497	Applicant(s) FITZGERALD ET AL.	
	Examiner Parithosh K. Tungaturthi	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 May 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 7-11, 13, 14, 16, 17 and 50-72 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 7-11, 13, 14, 16, 17 and 50-72 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The applicant has timely traversed the non-final rejection in the reply filed on 05/10/2007, and a response to the arguments is set forth.
2. Claims 5, 6, 12, 15 and 18-49 have been cancelled.
3. Claim 57 has been amended.
4. Claims 1-4, 7-11, 13, 14, 16, 17 and 50-72 are under examination.

Rejections Maintained

5. The rejection of claims 1-4, 7-11, 13-14, 16-17 and the newly added claims 70-72 under 35 U.S.C. 103(a) as being unpatentable over Ghetie et al (Cancer Res. 51:5876-5880, 1991; of record in the office action mailed 11/02/2000) and further in view of Shen et al (Int. J. Cancer 42:792-797, 1988; of record in the office action mailed 05/08/2002) and Reiter et al (Biochemistry 33:5451-5459, 1994; of record in the office action mailed 11/02/2000) and Kuan et al (Biochemistry 35:2872-2877, 1996, Abstract published 2/1/96; of record in the office action mailed 11/02/2000) and Orlandi et al (Proc. Natl. Acad. Sci. USA, 86:3833-3837, 1989; of record in the office action mailed 05/08/2002), Cabilly et al (U.S Patent 4816567, issued 3/89; of record in the office action mailed 08/02/2003), Boss et al (U.S Patent 4816397, issued 3/89; of record in the office action mailed 08/02/2003), Robinson et al (U.S. Patent 5618920, filed 4/94), Ward et al (Nature 341:544-546, 1989; of record in the office action mailed 08/02/2003), and Huston et al (U.S. Patent 5258498, issued 11/93; of record in the office action mailed 08/02/2003) is maintained.

The applicant argues that the designation "RFB4" by Shen et al provides no structural information regarding the sequence of the antibody ... the claims are patentable due to surprising and superior properties of the claimed RFB4-ds(Fv) immunoconjugates (page 7 of the response filed 05/10/2007). The applicant also argues that the improved binding affinity in the passage referred to by the examiner is relative to scFv, not relative to starting IgG. Dr. FitzGerald attests to the fact that the finding that RFB4 immunotoxins retain the binding specificity and affinity of the parent RFB4 IgG is unusual ... the superior binding properties and cytotoxicity of the claimed anti-CD22 immunoconjugates are unexpected and surprising. In addition, Dr. FitzGerald explains that the superior toxicity and efficacy of RFB4ds(Fv)-PE38 that was observed not only in animal models, but also in human Phase I trials ... the Examiner provides no evidence or reasoning as to why one of skill would predict such superior properties (page 8 of the response filed 05/10/2007).

The above arguments are carefully considered but are not found persuasive. As it has been stated before, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success that the antibody as claimed is obvious over the prior art because Ghetie et al teach the RFB4 anti-CD22 antibody conjugated to ricin A chain, Shen et al teach the hybridoma which produces the RFB4 antibody, Orlandi et al, Robinson et al, Cabilly et al & Huston et al together teach a general method for obtaining the VH and the VL genes and the amino acid sequence of an antibody by PCR from the hybridoma cell and because Reiter et al teach

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recombinant immunotoxins comprising disulfide stabilization with a cysteine at position 44 in the VH and a cysteine at position 100 in the VL. Secondly, in response to the argument that the claims are patentable due to surprising and superior properties of the claimed RFB4-ds(Fv) immunoconjugates, the applicant is reminded of the teachings of Reiter et al. Reiter et al teach that dsFv immunotoxins were stable in human serum and resistant to thermal and chemical denaturation (abstract, in particular). Further, Reiter et al teach that dsFv immunotoxins retain full activity at temperatures up to 42°C and retain significant activity at 45°C (page 701, 2nd column in particular), in addition to that disulfide-stabilized Fv immunotoxins retain full cytotoxic and binding activity (page 702, 2nd column in particular). Reiter et al also show that the dFv immunotoxins were active in vitro and in vivo and in one case dsFv immunotoxin was more active in vitro and in vivo than its single-chain counterpart (page 703, 1st column in particular).

It is noted that the applicant argues that Reiter et al teach the comparison of dsFv and scFv while Dr. FtizGerald compares the binding specificity and affinity of the dsFv with the parent RFB4 IgG to states that such properties of dsFv are surprising. However, it is the examiners position that such argument is irrelevant because it is well known in the art (Reiter et al, in particular) that dsFv molecules are highly stable and active both in vitro and in vivo. Hence, a skilled artisan would have a high expectation of success to produce a dsFv RFB4 antibody and be motivated to produce such an antibody because of its enhanced stability upon prolonged incubation in buffers and in human serum (page 703 of Reiter et al, 2nd column in particular). Reiter et al teach (page 704, in particular) that the dsFv molecules have increased stability to thermal and

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chemical denaturation, and that the thermostability of dsFv is an important factor in clinical applications, wherein dsFv immunotoxins are completely stable and active at 37°C.

The applicant argues that even though RFB4-dsFv may share common properties with other dsFv compounds ... the remarkable results in terms of retention of an affinity that is essentially the same as parent IgG and the clinical efficacy observed using the RFB4-dsFv constructs in patients is sufficient to render the claims patentable. (page 9 of the response filed

Such argument is not found persuasive, particularly because (i) Reiter et al (Biochemistry, page 5451 1st column in particular) teach that because of their small size, which facilitates tumor penetration, scFv molecules are potentially more useful than whole antibodies for the diagnosis and/or therapy of diseases such as cancer, where target antigens are expressed on the surface of malignant cells and (ii) since dsFv molecules are shown (as discussed above) to be stable in human serum and resistant to thermal and chemical denaturation, in addition to having increased stability as compared to scFv molecules; one of ordinary skill in the art would have been motivated to construct RFB4dsFv molecules. Thus, especially for clinical applications and since dsFv is more stable and resistant to thermal and chemical denaturation as compared to scFv which is shown to be more useful than whole antibodies, one of ordinary skill in the art would have had a high expectation of success to construct a RFB4-ds(Fv) which

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would result in a superior efficacy as compared to a whole antibody molecule (IgG, for example).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

6. Claims 57-69 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ghetie et al (Cancer Res. 51:5876-5880, 1991; of record in the office action mailed 11/02/2000) and further in view of Shen et al (Int. J. Cancer 42:792-797, 1988; of record in the office action mailed 05/08/2002) and Reiter et al (Biochemistry 33:5451-5459, 1994; of record in the office action mailed 11/02/2000) and Kuan et al (Biochemistry 35:2872-2877, 1996, Abstract published 2/1/96; of record in the office action mailed 11/02/2000).

The applicants argue that the conjugates exhibit surprising efficacy when used in vivo ... the office action provides no reasoning that the claimed methods would have been expected by one in the art to provide this exceptional level of efficacy in treating CD22+ B cell malignancies. (pages 9-10 of the response filed 05/10/2007).

The above arguments are carefully considered but are not found persuasive. The applicant is reminded that Ghetie et al teach the inhibition of growth of B-cell lymphomas in mice using RFB4 anti-CD22 antibody conjugated to ricin A chain. In addition, one skilled in the art would have furthermore be motivated to produce a

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method for inhibiting the growth of a malignant B-cell in vivo that expresses a CD22 molecule on the surface of the cell because Shen et al suggests that the unusually potent cytotoxic activity of RFB4 antibody would be excellent candidates for the systemic therapy of CD22⁺ human B-cell neoplasm; for example in B-cell lymphomas, hairy-cell leukemia and B-cell chronic lymphocytic leukemia in addition to making effective reagents for the in vivo therapy of CD22⁺ B cell lymphomas and leukemia in humans.

Thus, it is the examiners position that one of ordinary skill in the art would have been motivated and would have had a high expectation of success to construct the RFB4 dsFv anti-CD22 immunoconjugates and utilize them in vivo with successful clinical because Shen et al teach that RFB4 antibody would be excellent candidates for systemic therapy of CD22⁺ human B-cell neoplasm and Ghetie et al teach the inhibition of growth of B-cell lymphomas in mice using RFB4 anti-CD22 antibody conjugated to ricin A chain and because Reiter et al teach that the dsFv molecules have increased stability to thermal and chemical denaturation, and that the thermostability of dsFv is an important factor in clinical applications.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

7. No claims are allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.


9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi
(571) 272-8789



DAVID J. BLANCHARD
PATENT EXAMINER
PRIMARY